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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Williams, A., et al.	Confirmation No. 6889
Serial No.: 09/410,462	Art Unit: 1635
Filing Date: 1 October 1999	Examiner: J.E. Angell
Title: A SINGLE AGENT METHOD FOR KILLING TUMOR AND TUMOR ASSOCIATED ENDOTHELIAL CELLS USING ADENOVIRAL MUTANTS	

REPLY BRIEF UNDER 37 C.F.R. § 41.41(a)(1)

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Dear Sir:

Introductory Remarks

This is in response to the Examiner's Answer, mailed 29 September 2010. Per M.P.E.P. §1208 (Eighth Edition) this Reply Brief contains the following:

(A) Identification page setting forth the Appellants' name(s), the application number, the filing date of the application, the title of the invention, the name of the Examiner, the art unit of the Examiner and the title of the paper (i.e., Reply Brief);

(B) Status of claims page(s);

(C) Grounds of rejection to be reviewed on appeal page(s); and

(D) Argument page(s).

Status of the Claims

Claims 6-11, 15, 17-20, 28, and 34 are pending. Claim 28 is allowed. Claims 8-10, 19, 20, and 34 are objected to. Claims 6, 7, 11, 15, 17, and 18 are rejected.

The rejection of claims 6, 7, 11, 15, 17, and 18 is appealed herein.

Grounds of Rejection To Be Reviewed on Appeal

Sole Issue

In the final Office action, mailed 07 April 2009, the Examiner rejected claims 6, 7, 11, 15, 17, and 18 under 35 U.S.C. §102(e), asserting that the claims are anticipated by U.S. Patent No. 6,080,578 (Bischoff, et al., previously of record), for the reasons of record. (Office action, mailed 07 April 2009, page 2.)

Argument

This Reply Brief is filed in view of section (10) of the Examiner's Answer, mailed 29 September 2010.

Appellants note the Examiner's improper reliance on *In re Spada, et al.*, and *In re Von Schickh*, This case law is cited by the Examiner in the Examiner's Answer, mailed 29 September 2010. *In re Spada, et al.*, deals only with the novelty of compositions. All of the present claims are method claims. The Federal Circuit in *In re Spada, et al.*, stated the following:

> The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 780, 782, 227 USPQ 773, 777-78, 778 (Fed.Cir.1985); *In re Pearson*, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974); *In re Lemin*, 326 F.2d 437, 440, 140 USPQ 273, 276 (CCPA 1964). Thus, the initial inquiry is to the novelty of the composition. Titanium Metals, 778 F.2d at 780, 227 USPQ at 777. (*In re Spada, et al.*, 911 F.2d 705, 15 U.S.P.Q.2d 1655 (Fed. Cir. 1990))

Accordingly, the holding in *In re Spada, et al.*, has no bearing in the present case because it related to the novelty of a composition, not the performance of a method.

Regarding in *In re Von Schickh*, the Examiner's reliance is clearly improper because the issue was obviousness under 35 U.S.C. §103(a), not anticipation; further, the CCPA affirmed the unobviousness of the invention and reversed the Board. The CCPA in *In re Von Schickh*, stated the following:

> In summary, viewing both what appellant did and what he obtained in light of the prior art relied on, we conclude that the invention as a whole is unobvious within the meaning of 35 U.S.C. § 103. The decision of the board is reversed. (*In re Von Schickh*, 362 F.2d 821 (CCPA 1966))

Further, regarding *Integra Life Sciences I Ltd. v. Merck KGaA*, the Examiner asserts the following:

> Moreover, the court in *Integra Life Sciences I Ltd. v. Merck KGaA*, 50 USPQ2d 1846 (DC SCalif, 1999) held that a reference teaching a process may anticipate claims drawn to a method comprising the same process steps, despite the recitation of a different intended use in the preamble or the later discovery of a particular property of one of the starting materials or end products. (Examiner's Answer, mailed 29 September 2010, pages 7-8.)

The essence of this issue was previously raised by the Examiner in the Advisory Action but was not maintained in the subsequent Office action (*see* Advisory Action, mailed 25 October 2007; Brief on Appeal, filed 23 February 2008; and Office action, mailed 16 June 2008). Appellants previously addressed this issue (*see* Brief on Appeal, filed 23 February 2008, pages 20-21) as follows. The holding regarding inherency in *Integra Life Sciences I Ltd. v. Merck KGaA* was discussed by the U.S. District Court as follows:

> The court will not and need not address whether the alleged preamble language of Claim 2 is or is not an "express limitation" of the Claim. Even assuming, arguendo, that the preamble to Claim 2 does expressly limit the claimed invention, the undisputed facts and methods underlying plaintiff's claimed-invention still remain the same: plaintiff's Nature paper explicitly described the role of certain RGD peptides in preventing kidney cells from attaching to a substrate which essentially shut down all cell growth or proliferation. The portion of the *'621 Patent* specification upon which Claim 2 relies describes a similar, if not identical, assay using the same peptide (GRGDSP) to detach the same type of cells (NRK cells) from an analogous substrate which, as it turns out, permanently keeps them from reattaching (or proliferating). *'621 Patent* at Col. 7, lines 18-34, 63-68. (*Integra Life Sciences I Ltd. v. Merck KGaA*, 1999 U.S. Dist. LEXIS 10380, *17, 50 USPQ2d 1846 (DC SCalif, 1999); emphasis added.)

In the present case, the reference of Bischoff, et al., teaches administration of mutant adenovirus to tumor cells that have lost RB gene function to effect killing of the $RB^{(-)}$ tumor cells. The method claims of the present method require direct administration of mutant adenovirus to endothelial cells and such administration is effective regardless of the RB-expression status of any associated tumor cells. That is, the reference of Bischoff, et al., does not explicitly describe the role of mutant adenovirus in selective killing of dividing endothelial cells independent of RB-expression status (contrary to the fact pattern of *Integra Life Sciences I Ltd. v. Merck KGaA*).

The Examiner goes on to discuss the physical location of the endothelial cells, with reference to Appellants' Appeal Brief; however, as previously discussed by Appellants (*see* Appeal Brief filed 31 August 2009, pages 15-16), the truth of the matter is that the reference of Bischoff, et al., lacks descriptive matter related to killing of dividing endothelial cells by direct administration of a mutant adenovirus. Although Bischoff, et al., teach administration of recombinant adenovirus to infect neoplastic cells, in the absence of the teachings of the present specification, one of ordinary skill in the art would not be guided to use replication competent adenovirus to preferentially kill dividing endothelial cells relative to killing of quiescent endothelial cells, which in and of itself provides an

art recognized cancer treatment (i.e., disruption of tumor angiogenesis) that is distinct from direct killing of tumor cells (i.e., neoplastic cells).

Also as previously noted by Appellants (*see* Appeal Brief filed 31 August 2009, pages 16-17), the Federal Circuit stated that "[a] reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Laboratories, Inc.,* 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001). The reference of Bischoff, et al., teaches only the killing of $RB^{(-)}$ tumor cells by administration of replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region to the $RB^{(-)}$ tumor cells. Here, the claimed invention is not a natural result flowing from the reference of the Bischoff, et al., because the reference contains no explicitly explicated limitations from which the natural result flowing from the reference's teachings would result in the use of the described adenoviral vectors as an alternative method of controlling tumor growth, that is, direct administration of mutant adenovirus to endothelial cells for preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably microvascular endothelial cells.

Finally, in the Reply Brief the Examiner purported the following:

> In response to applicant's argument that it is not inherent to infect endothelial cells or other types (non-$RB^{(-)}$) tumor cells with the mutant adenovirus, it is noted that (1) intravenous administration of the adenovirus would necessarily result in the adenovirus directly contacting endothelial cells as endothelial cells line the interior of blood vessels, and (2) the rejected claims do not required that the adenovirus is administered to any specific type of tumor (i.e., there is no requirement in the claims the adenovirus is administered to non-$RB^{(-)}$ tumor cells). (Examiner's Answer, mailed 29 September 2010, pages 9-10.)

First, the Examiner's assertion that "intravenous administration of the adenovirus would necessarily result in the adenovirus directly contacting endothelial cells as endothelial cells line the interior of blood vessels" is misleading. As previously discussed in Appellants' Appeal Brief (*see* Appeal Brief filed 31 August 2009, page 17), in a situation where a target tumor (regardless of RB-expression status of the tumor cells) did not respond to direct killing of neoplastic cells by a selected method (*e.g.*, chemotherapy), in view of the teachings of the present specification one of ordinary skill in the art may choose to administer a mutant adenovirus to the dividing endothelial cells to reduce or eliminate angiogenesis which provides a blood supply to a tumor. The teachings of Bischoff, et al., would not direct one of ordinary skill in the art to such an approach. Inherency must flow as a necessary conclusion from the prior art, not simply a possible one. "The mere fact that a

certain thing may result from a given set of circumstances is not sufficient [to establish inherency.]" *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (C.C.P.A. 1981). Moreover, the present application discloses a relationship that was not recognized by those reasonably skilled in the art, that is the administration of mutant adenovirus to endothelial cells for preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. As such, Appellants submit that the pending claims define a patentable invention. Accordingly, the teachings of the reference of Bischoff, et al., do not inherently anticipate the claimed invention.

Second, the Examiner is correct that the claim does not require that adenovirus be administered to any specific type of tumor, rather the claims are generally directed to killing dividing endothelial cells, which is not taught by the reference of Bischoff, et al. It is unclear why the Examiner raises this issue. Further, it is unclear why the Examiner states "[a]lthough the claims are interpreted in light of the specification, limitations from the specification are not read into the claims" because the claims recite selective killing of dividing endothelial cells. No reliance on the specification is necessary to interpret this limitation.

In conclusion, as previously discussed in Appellants' Appeal Brief, on page 19, the reference of Bischoff, et al, does not expressly or inherently teach all of the claimed elements of methods of the present invention, for example, as follows:

- The reference does not teach endothelial cells.
- The reference does not teach administration of a replication competent adenovirus, comprising a mutation in an E1A CR2 RB family member binding region, to endothelial cells.
- The reference does not teach preferential killing of dividing endothelial cells compared to quiescent endothelial cells by administration of such mutant adenovirus.
- The reference teaches only methods for specifically ablating $RB^{(-)}$ tumor cells by infecting $RB^{(-)}$ tumor cell populations with a E1A-$RB^{(-)}$ replication defective adenovirus mutants; that is, the reference does not teach administration of such mutant adenovirus for preferential killing of dividing endothelial cells in cell populations without regard to RB-expression status of the cells in the population.
- The reference does not teach that such mutant adenovirus replicates to higher titers in the dividing endothelial cells versus wild-type adenovirus.
- The reference does not teach controlling angiogenesis in an animal by infection of

dividing endothelial cells with such mutant adenovirus.

Conclusion

In light of the foregoing, Appellants' Appeal Brief, the teachings of the specification, and the level of skill of one of ordinary skill in the art, Appellants respectfully request the Board to reverse the rejection by the Examiner in this Application.

Respectfully submitted,

Date: 28 October 2010 By: /Gary R. Fabian/

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Appellants

Customer No. 037499
ONYX Pharmaceuticals, Inc.
2100 Powell Street
Emeryville, CA 94608
Phone: (510) 597-6502
Facsimile: (510) 597-6693